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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/111,123	07/06/1998	HABIB ZAGHOUANI	ALLIA143	5474

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EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/111,123	ZAGHOUANI, HABIB	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-27* is/are pending in the application.

4a) Of the above claim(s) *8-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-7 and 21-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on June 1, 2004 have been entered.

Claims 1 and 3-27 are pending.

Claims 8-20 are withdrawn from consideration.

Claim 2 is canceled.

The prior rejection of claims 1-7 under 35 U.S.C. 112, first paragraph is vacated. As such, Applicant's arguments, filed 6/1/2004, are acknowledged but are moot and have not been considered.

Priority

2. Applicant needs to update the status of the priority documents in the specification to include the issuance of patent 6,737,057 from application 08/779,767.

Claim Objections

3. Claims 4 and 23 are objected to because of the following informalities: The autoimmune disease lupus is misspelled. Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 3-7 and 21-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

These claims recite the use of a fusion protein containing an antagonist peptide to alleviate symptoms associated with any autoimmune disorder, but the specification only discloses the use of two antagonists. The antagonist derived from proteolipid protein and is found in the specification and the antagonist from myelin basic protein in is found in Applicant's declaration of July 5, 2001, both of which are used in the treatment of experimental allergic encephalomyelitis (EAE), a murine model of multiple

sclerosis. The number of autoimmune diseases is large, with great differences seen in their etiology and progression. These differences account for the larger number of known autoantigens, many of which appear to be unrelated in structure, and the antagonist peptides that can be derived from said autoantigens is even larger. The specification does not appear to contain a representative list of antagonists derived from autoimmune diseases, nor does it appear to contain a description of a common structure that is present in all antagonists derived from autoantigens. Thus it appears that applicant has claimed a broad genus of fusion proteins that contain T cell receptor antagonists, with the identity of the antagonists being defined only through their activity as an antagonist of autoreactive T cells. In University of California v. Eli Lilly and Co. (CAFC) 43 USPQ2d 1398, the court noted:

> "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene (in the instant case, a peptide) does, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes (peptides) may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material."

Therefore, there appears to be insufficient description in the specification for a person of skill in the art to know what defines an antagonist from an autoantigen associated with a particular autoimmune disorder that could be used in the full breadth of the products envisioned by the claimed invention.

6. Claims 1, 3-7 and 21-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the alleviation of autoimmune symptoms in the murine EAE model, does not reasonably provide enablement for the alleviation of any symptom associated with any autoimmune disorder. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's invention is a fusion protein consisting of a T cell receptor antagonist fused to an immunoglobulin. The intended use for this compound is that it can be given to a patient to alleviate symptoms associated with an autoimmune disorder and to prevent the activation of T cells specific for the T cell receptor antagonist of the invention. Applicant has provided clear guidance and working examples that demonstrate the ability to alleviate autoimmune symptoms in the EAE model system. In that system, when mice suffering from EAE were treated with an immunoglobulin containing the proteolipid antagonist peptide, the mice experienced an alleviation of symptoms and failed to relapse during the course of the experiment. However, insufficient data is presented in the specification and declarations to verify that Applicant's invention can enable the breadth of the claims by treating any autoimmune disorder in any organism. Applicant specifically claims his invention to be useful in treating the diseases listed in claims 4 and 23, but insufficient guidance is provided concerning the identity of the antagonist to be used in the claimed diseases other than

for antagonists derived from proteolipid protein and myelin basic protein in the case of EAE. EAE is an established laboratory model for multiple sclerosis, the prior art teaches that agents useful for the treatment of EAE have not been effective when given to human patients for the treatment of multiple sclerosis (see Pender and Wolfe, Intern Med J., 2002, 32:554-63, entire article, abstract in particular), and that in general there has been limited success in developing antigen-specific therapies for autoimmune disorders (Steinman, Science, 2004, 305:212-216, see entire document, especially p215, first column, third full paragraph and Tisch et al., PNAS, 1994, p437-438, see entire document). As such, it is clear from the prior art that the treatment of autoimmune disorders is not predictable.

Further, it is unclear from the specification how Applicant can "prevent" the activation of autoreactive T cells specific for a given T cell receptor antagonist using his invention. T cells can be activated nonspecifically through various mechanisms including bystander activation (Eberl et al., J. Immunol., 2000, 165:4305-4311, see entire document, especially abstract), and can respond to the presentation of peptide sequences that share common structural features through the phenomenon known as molecular mimicry (Wucherpfennig and Strominger, Cell, 1995; 80:695-705, see entire document, abstract in particular). Thus, in the absence of data to the contrary, it is not clear that the autoreactive T cells specific for the proteolipid protein antagonist in the mouse EAE model, or autoreactive T cells specific for an antagonist in general, are rendered incapable of being activated under any circumstance, a requirement for truly preventing activation. Moreover, the claims specifically recite "for the alleviation of

symptoms associated with an autoimmune disorder". If a patient shows symptoms associated with an autoimmune disorder, autoreactive T cells in the patient have already been activated, thus it is not possible to "prevent" an event that has already occurred.

Thus, given the nature of the invention, the breadth of the claims, the limited number of working examples, the limited guidance as to the identity of antagonists in the specification, and the difficulty in alleviating autoimmune symptoms and preventing autoreactive T cell activation based on the prior art, an undue amount of experimentation would be required before a person of skill in the art could practice the invention as claimed.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 1, 3-4, and 21-24 are rejected under 35 U.S.C. 102(e) as being anticipated by Deo et al., U.S. Patent Number 5,837,243. Deo et al. teach

> "(a) antigenic peptides genetically grafted onto the constant region of an anti-Fc.gamma.RI antibody are significantly more efficient in antigen presentation of the antigen and T cell stimulation compared to the antigen alone, and (b) that antagonistic peptides genetically grafted onto the constant region of an anti-Fc.gamma.RI are significantly more efficient in inhibiting T cell stimulation compared to the antagonistic peptide alone. Thus, such fusion proteins will effectively increase the delivery of peptides to antigen presenting cells (APCs) in vivo and will be useful in various therapeutic methods." (See entire document, especially column 27, lines 31-37.)

The peptide fused to an Ig constant region in example 7 of Deo et al. is presented in the context of MHC Class II molecules (column 32, lines 20-25), and said constant region is capable of binding an Fc receptor and being endocytosed to enhance antigen presentation (column 30, lines 55-59 and column 31, lines 21-24). Autoimmune diseases disclosed that would be amenable to treatment with such a molecule include rheumatoid arthritis, multiple sclerosis, and lupus (column 11, line 19, and column 33, first full paragraph, especially lines 16-17). Deo et al. also disclose that engineering peptides into the constant domain of a human immunoglobulin represents a general approach to increase antigenic potency (column 33, lines 2-6), and the immunoglobulin used in Example 7 is humanized (column 29, line 16-17). Therefore, the prior art teachings anticipate the claimed invention.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1, 5, 21 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Deo et al., U.S. Patent Number 5,837,243 in view of Karin et al. (J. Exp. Med, 1994, 180: 2227-2237).

Deo et al. teaches that an immunoglobulin containing an antagonist peptide can be used as an antigen-specific therapy for autoimmune diseases for the reasons cited previously in this Office Action.

Deo et al. does not specify the sequence nor the origin of the peptide used for the autoimmune therapy.

Karin et al. teaches the use of T cell receptor antagonist peptides derived from myelin basic protein for the treatment of EAE.

A person of ordinary skill in the art would have been motivated at the time the invention was made to insert the T cell receptor antagonist peptides of Karin et al. in the fusion construct of Deo et al. for the treatment of EAE because a construct containing antagonist peptides in an immunoglobulin as taught by Deo et al. would have the advantage of increased antigenic potency for the treatment of disease (column 33, lines 2-6) over peptide therapy alone as taught by Karin et al.

11. Claims 1, 6, 21 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Deo et al., U.S. Patent Number 5,837,243 in view of Kuchroo et al., (J. Immunol. 1994, 153: 3326-3336).

Deo et al. teaches that an immunoglobulin containing an antagonist peptide can be used as an antigen-specific therapy for autoimmune diseases for the reasons cited previously in this Office Action.

Deo et al. does not specify the sequence nor the origin of the peptide used for the autoimmune therapy.

Kuchroo et al. teaches T cell receptor antagonist peptides derived from myelin proteolipid protein for the treatment of EAE.

A person of ordinary skill in the art would have been motivated at the time the invention was made to insert the T cell receptor antagonist peptides of Kuchroo et al. in the fusion construct of Deo et al. for the treatment of EAE because a construct containing antagonist peptides in an immunoglobulin as taught by Deo et al. would have the advantage of increased antigenic potency for the treatment of disease (column 33, lines 2-6) over peptide therapy alone as taught by Kuchroo et al.

12. Claims 1,7, 21 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Deo et al., U.S. Patent Number 5,837,243 in view of Elliott et al. (J. Clin. Invest., 1996, 98: 1602-1612), Kuchroo et al., (J. Immunol. 1994, 153: 3326-3336) and Karin et al. (J. Exp. Med, 1994, 180: 2227-2237).

Deo et al. teaches that an immunoglobulin containing an antagonist peptide can be used as an antigen-specific therapy for autoimmune diseases for the reasons cited previously in this Office Action. Deo et al. does not specify the sequence nor the origin of the peptide used for the autoimmune therapy.

Kuchroo et al. discloses T cell receptor antagonist peptides derived from proteolipid protein, while Karin et al. discloses T cell receptor antagonist peptides derived from myelin basic protein. Both sets of antagonists are useful in treating EAE.

Elliott et al. teaches that a construct containing multiple epitopes will be more effective than the use of a single epitope in treating EAE (see entire document, particularly page 1611, first and second full paragraphs, left column).

A person of ordinary skill in the art would have been motivated at the time the invention was made to include more than one peptide epitope into the invention of Deo et al., using the antagonist peptides disclosed by Kuchroo et al. and Karin et al., because Elliott et al. teaches the advantages of simultaneously targeting multiple epitopes in the course of treating an autoimmune disease, and Deo et al. teaches fusion constructs containing peptide antagonists are better for treatment purposes than peptide therapy alone because of increased antigen potency.

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 1, 3-4, 6, 21-24 and 26 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 6,737,057. Although the conflicting claims are not identical, they are not patentably distinct from each other.

The claims of U.S. Patent No. 6,737,057 teach a composition comprising an immunoglobulin linked to a peptide that can bind an Fc receptor, be endocytosed, processed and presented in the context of MHC Class II molecules for the purpose of preventing the activation of autoreactive T cells *in vivo*. The claims of U.S. Patent No. 6,737,057 also teach the use of a human immunoglobulin protein and the incorporation of a T cell antagonist from proteolipid protein. The claims of the instant application recite a fusion protein for the treatment of an autoimmune disorder comprising an

immunoglobulin linked to a peptide that can bind an Fc receptor, be endocytosed, processed and presented in the context of MHC Class II molecules for the purpose of preventing the activation of autoreactive T cells. Patients have symptoms associated with an autoimmune disorder that require alleviation, thus necessitating that the fusion protein of the instant application be used *in vivo*. The fusion protein of the instant application cannot be administered to a patient for the treatment of an autoimmune disorder without first placing it into a solution or adding it into a pill, thus making it a composition. Therefore, the instantly pending claims are obvious in view of claims 1-16 of U.S. Patent No. 6,737,057.

15. No claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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July 27, 2004

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